Dyslipidemia

(Med-341)

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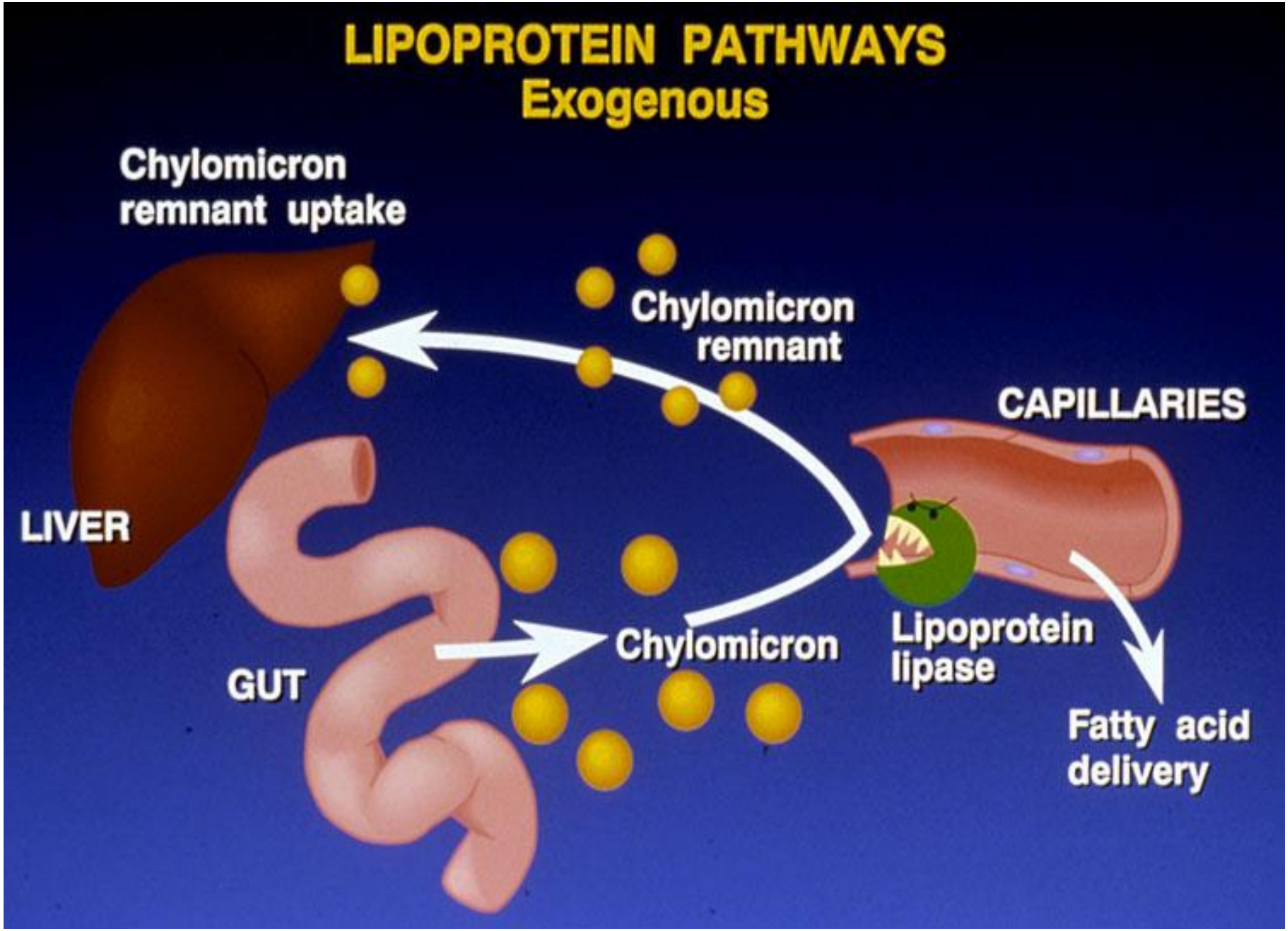
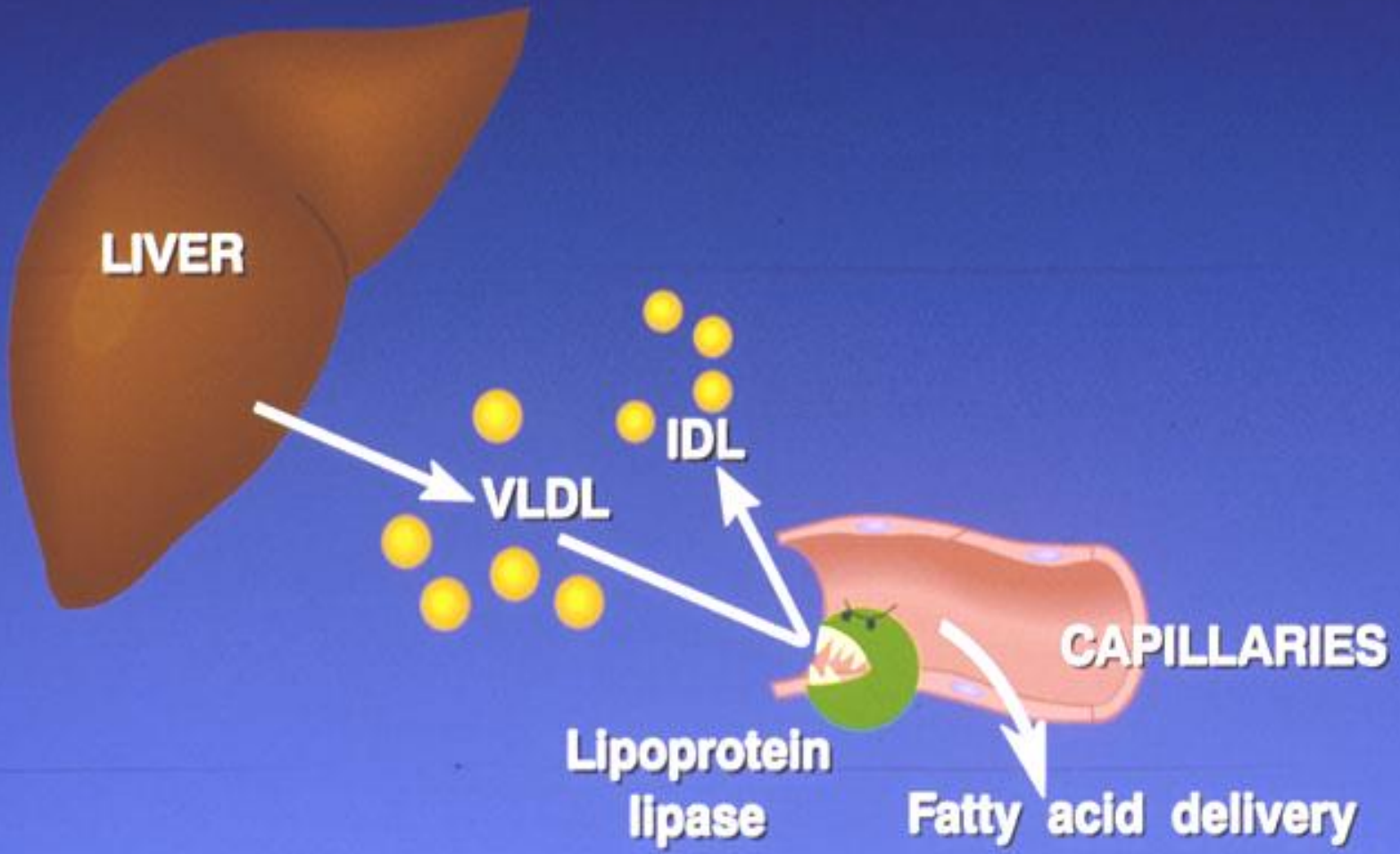
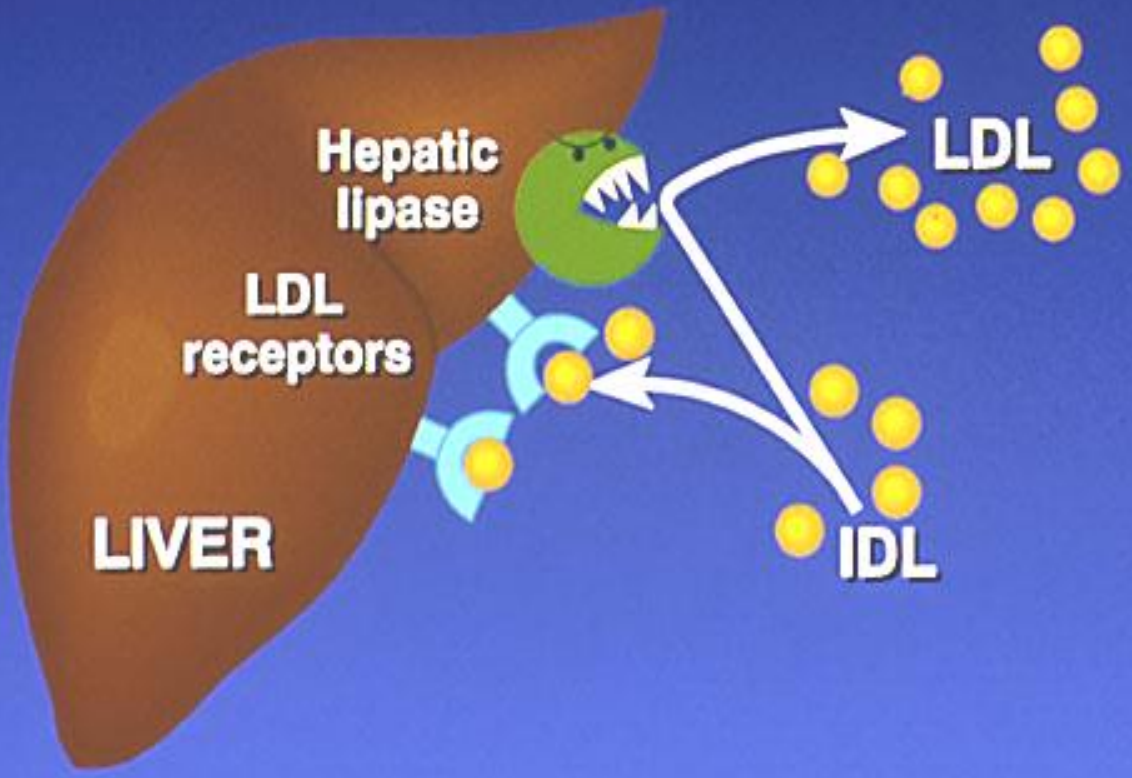
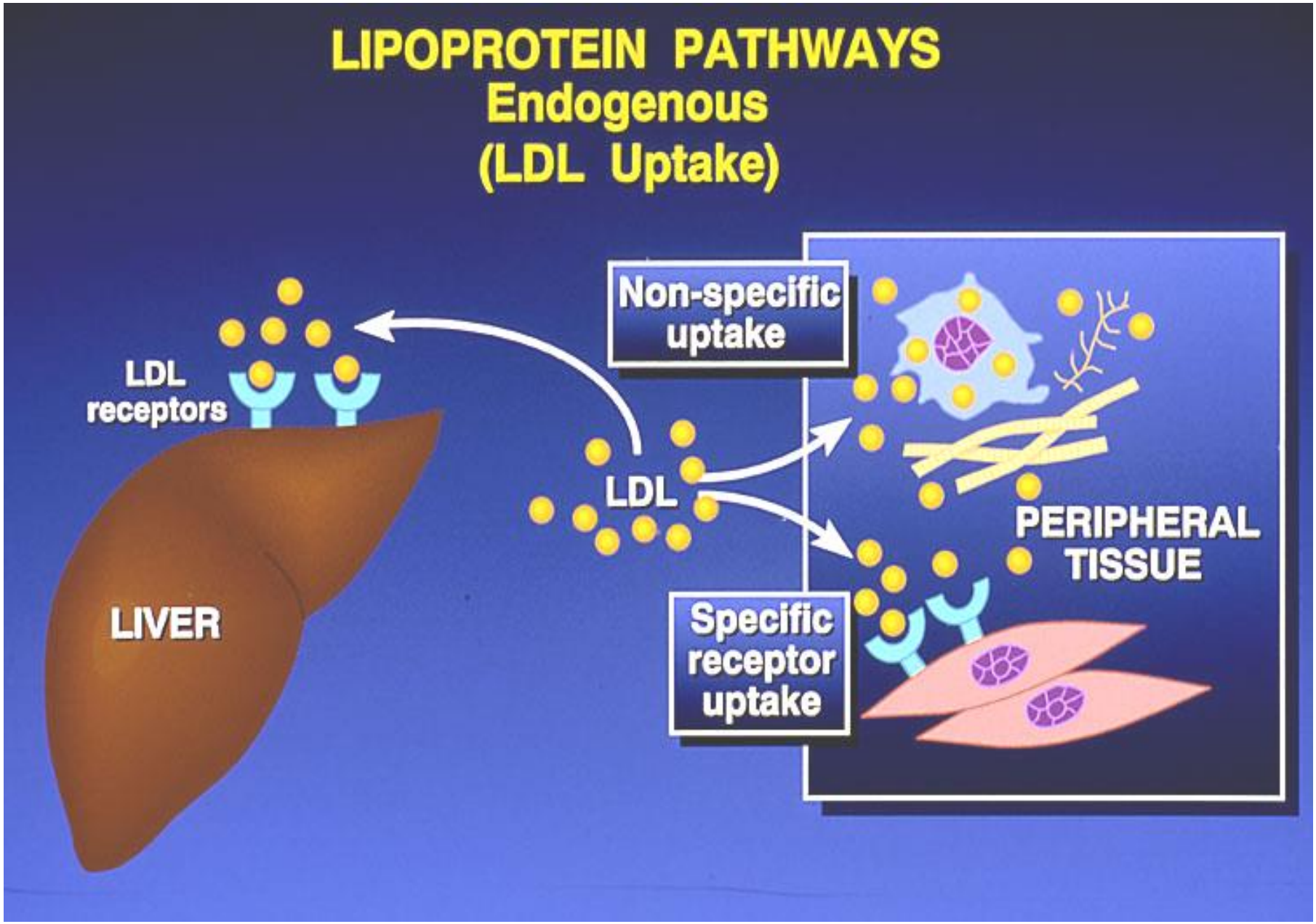

LIPOPROTEIN PATHWAYS
Exogenous
Chylomicron remnant uptake
Chylomicron remnant
CAPILLARIES
LIVER
GUT
Chylomicron
Lipoprotein lipase
Fatty acid delivery

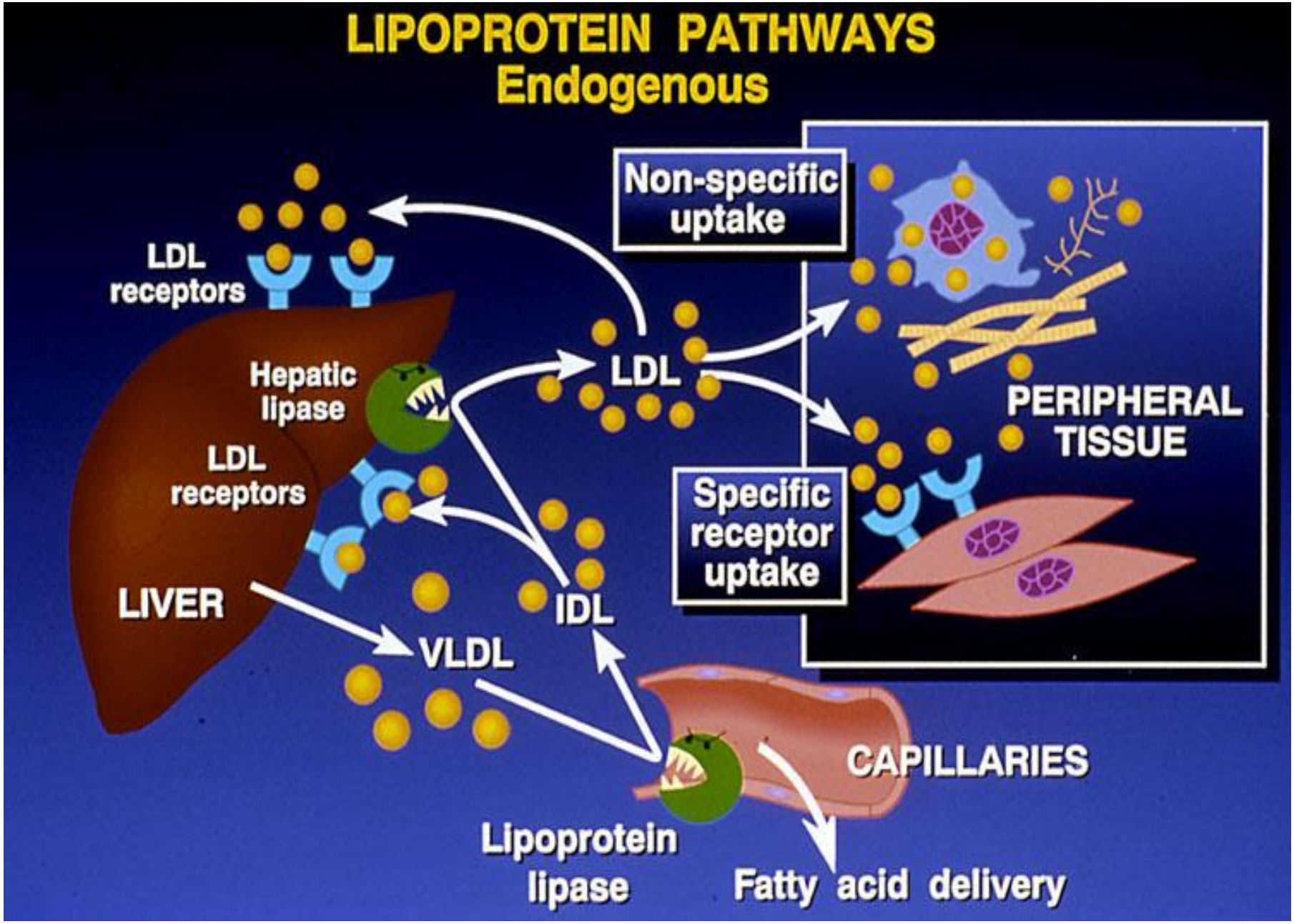
LIPOPROTEIN PATHWAYS
Endogenous
(VLDL-IDL)



LIPOPROTEIN PATHWAYS
Endogenous
(IDL-LDL)




LIPOPROTEIN PATHWAYS
Endogenous
(LDL Uptake)
Non-specific uptake
LDL receptors
LDL
PERIPHERAL TISSUE
LIVER
Specific receptor uptake


LIPOPROTEIN PATHWAYS
Endogenous
Non-specific uptake
LDL receptors
Hepatic lipase
LDL
PERIPHERAL TISSUE
LDL receptors
Specific receptor uptake
LIVER
IDL
VLDL
CAPILLARIES
Lipoprotein lipase
Fatty acid delivery

The story of lipids

- Chylomicrons transport fats from the intestinal mucosa to the liver
- In the liver, VLDL released to blood stream to form LDL, IDL and LDL.
- LDL then carries fat and cholesterol to the body's cells. LDL receptors in Liver take the LDL to Liver.
- High-density lipoproteins (HDL) released from intestine and liver and carry fat and cholesterol from blood vessels to the liver.

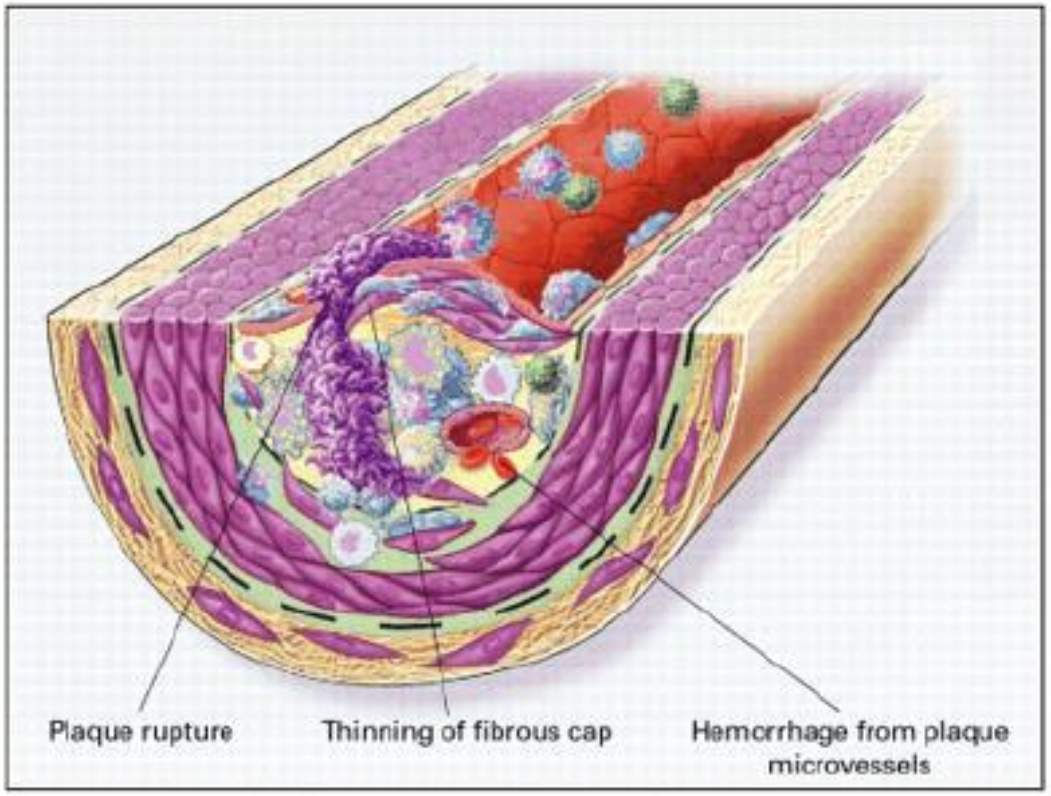
The story of lipids (cont.)

- When oxidized LDL cholesterol gets high, atheroma formation in the walls of arteries occurs, which causes atherosclerosis.

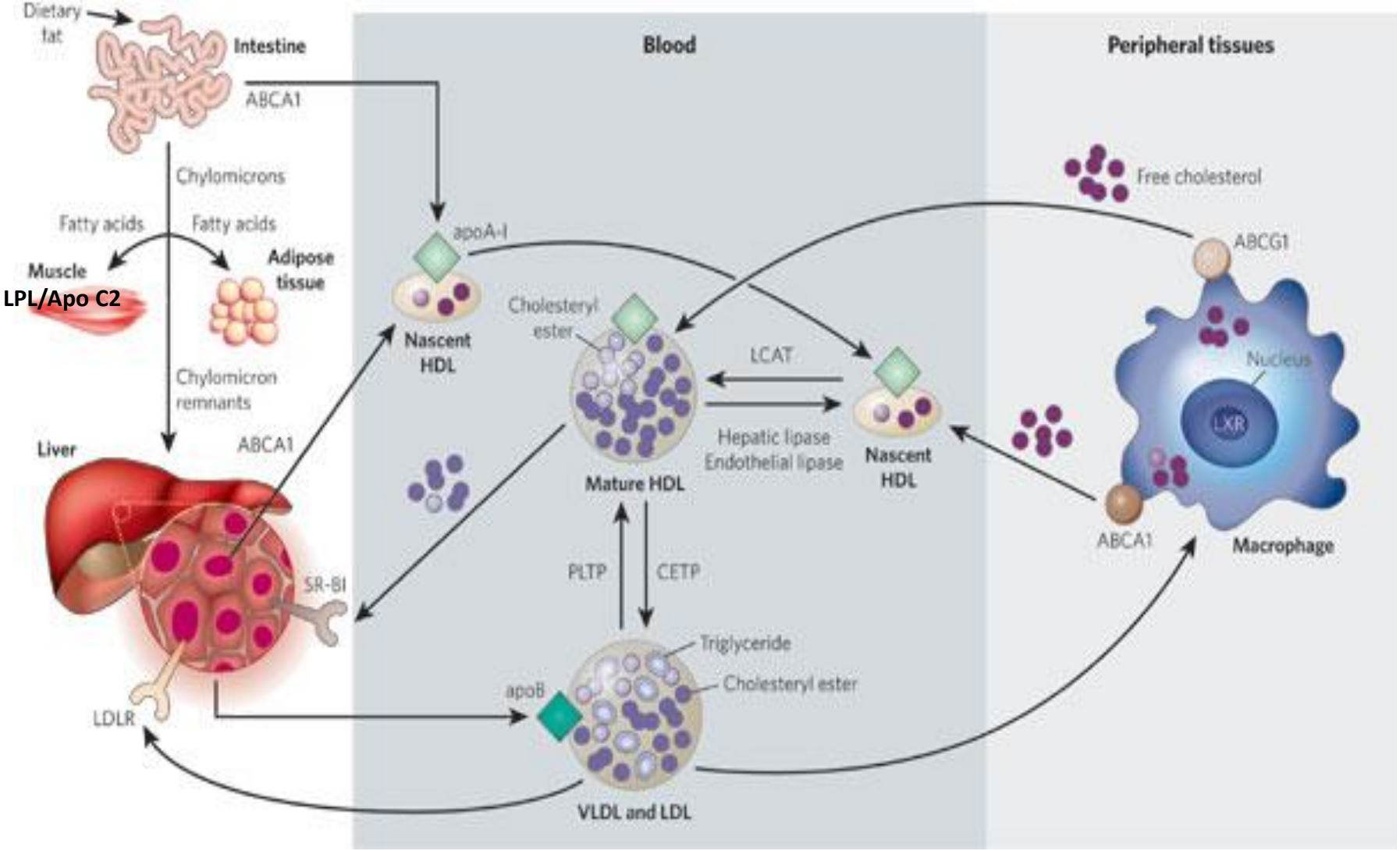
- HDL cholesterol is able to go and remove cholesterol from the atheroma.

- Atherogenic cholesterol → LDL, VLDL, IDL

Atherosclerosis

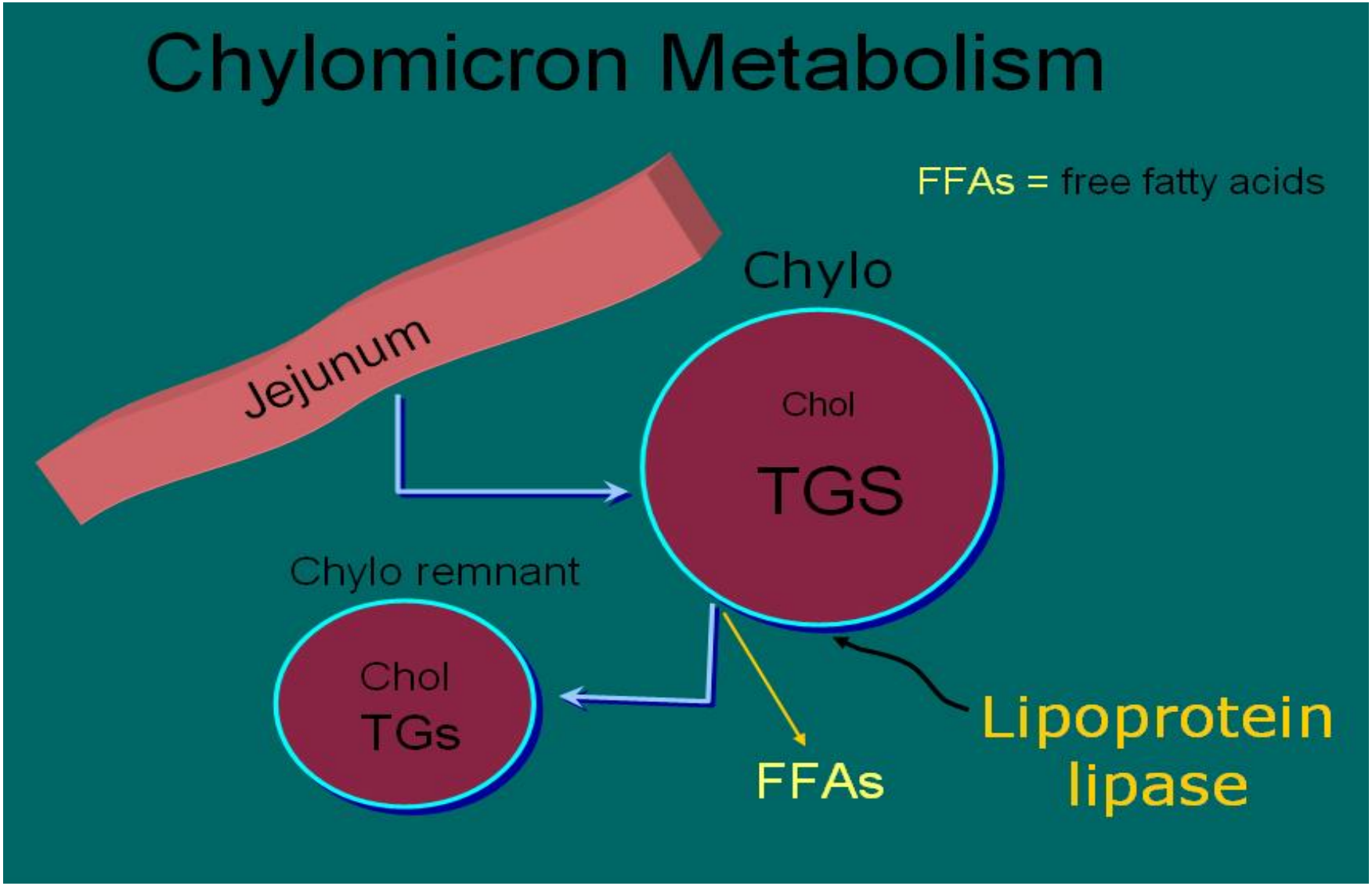


Lipid Transport

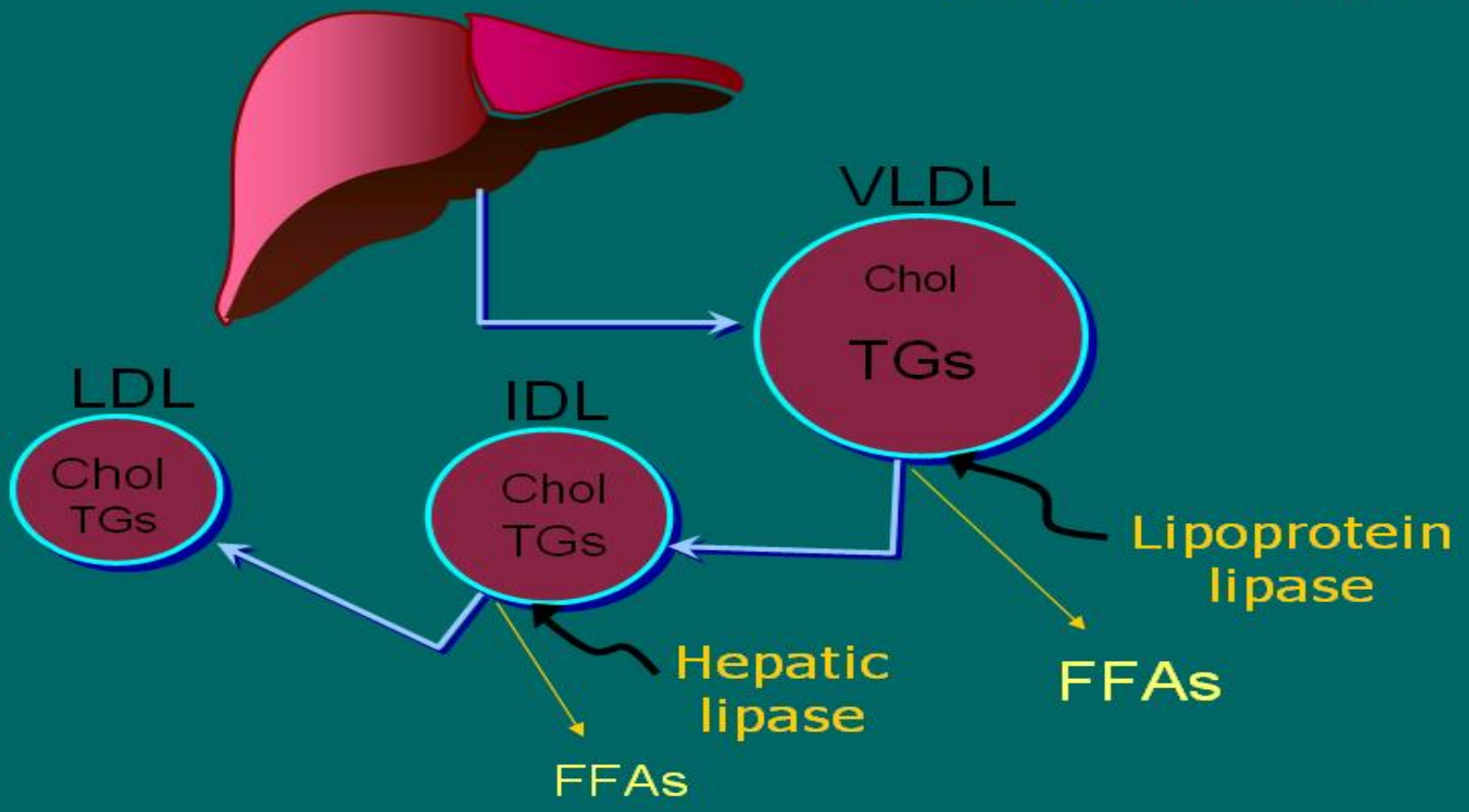


Rader DJ, Daugherty, A Nature 2008; 451:904-913

Chylomicron Metabolism

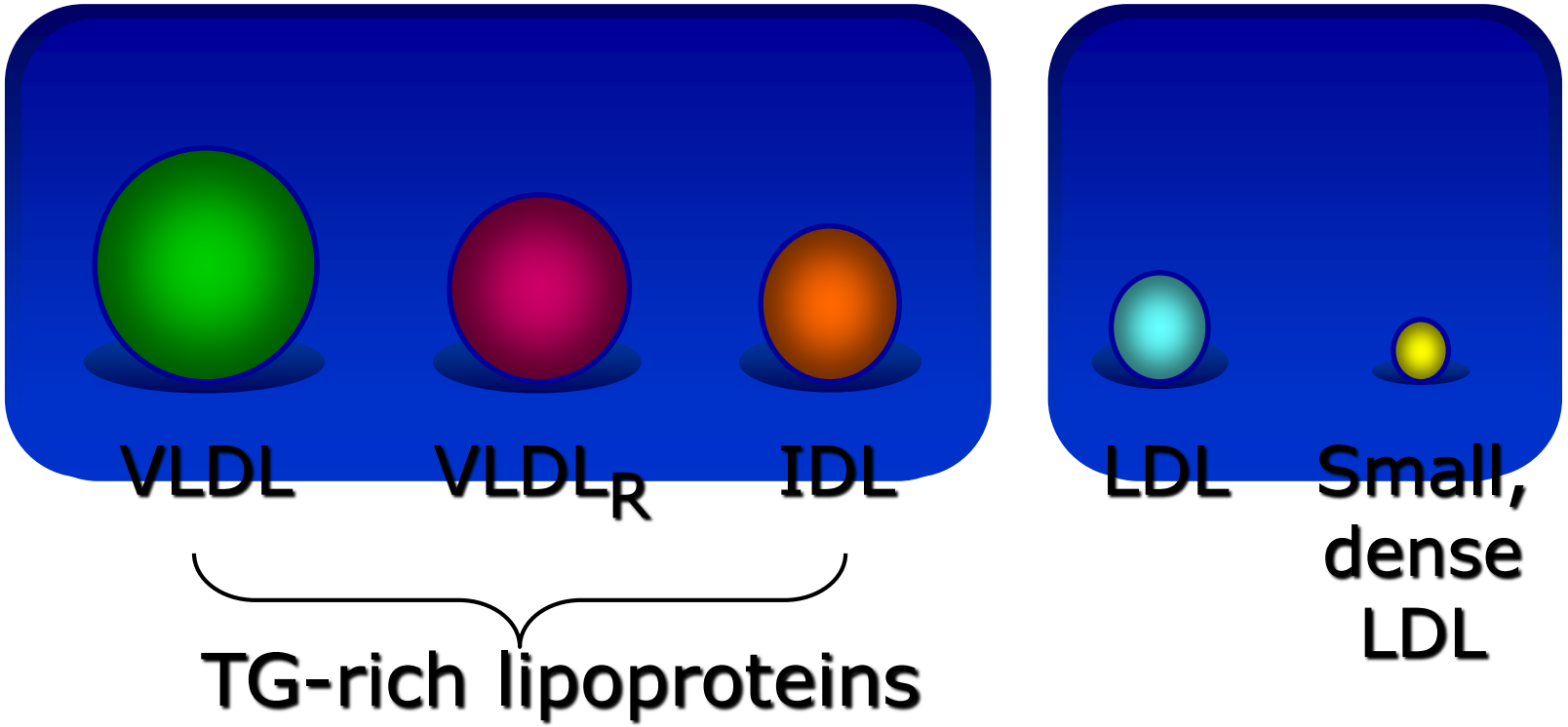


VLDL Metabolism

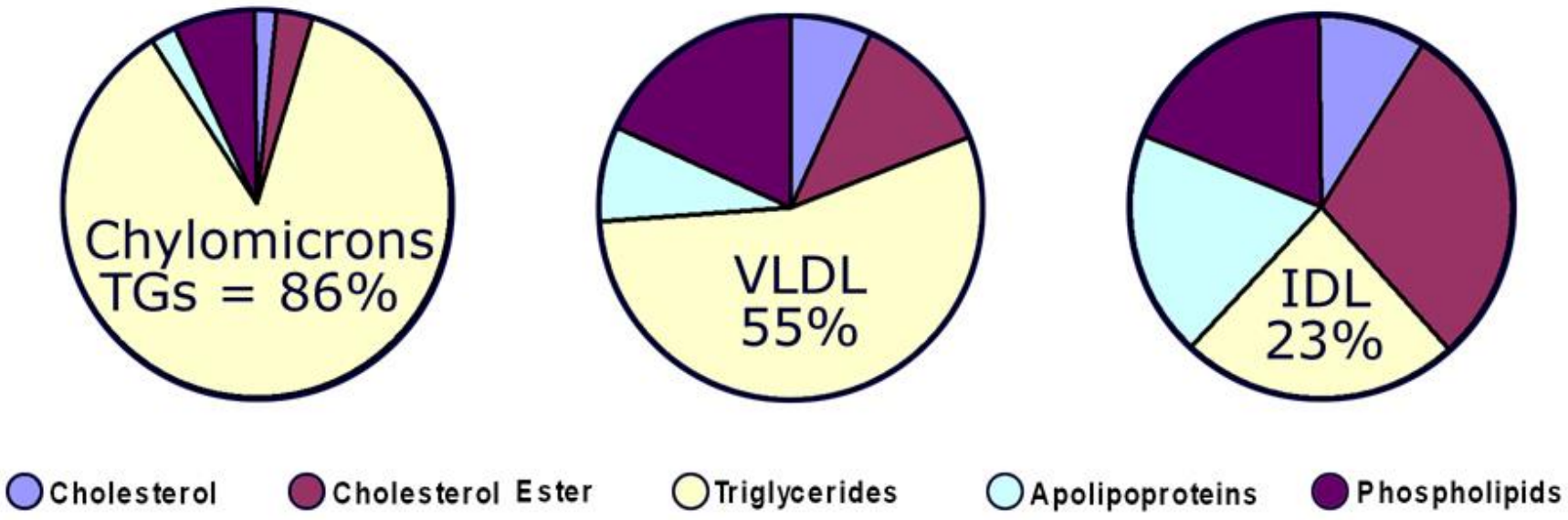


Atherogenic Particles

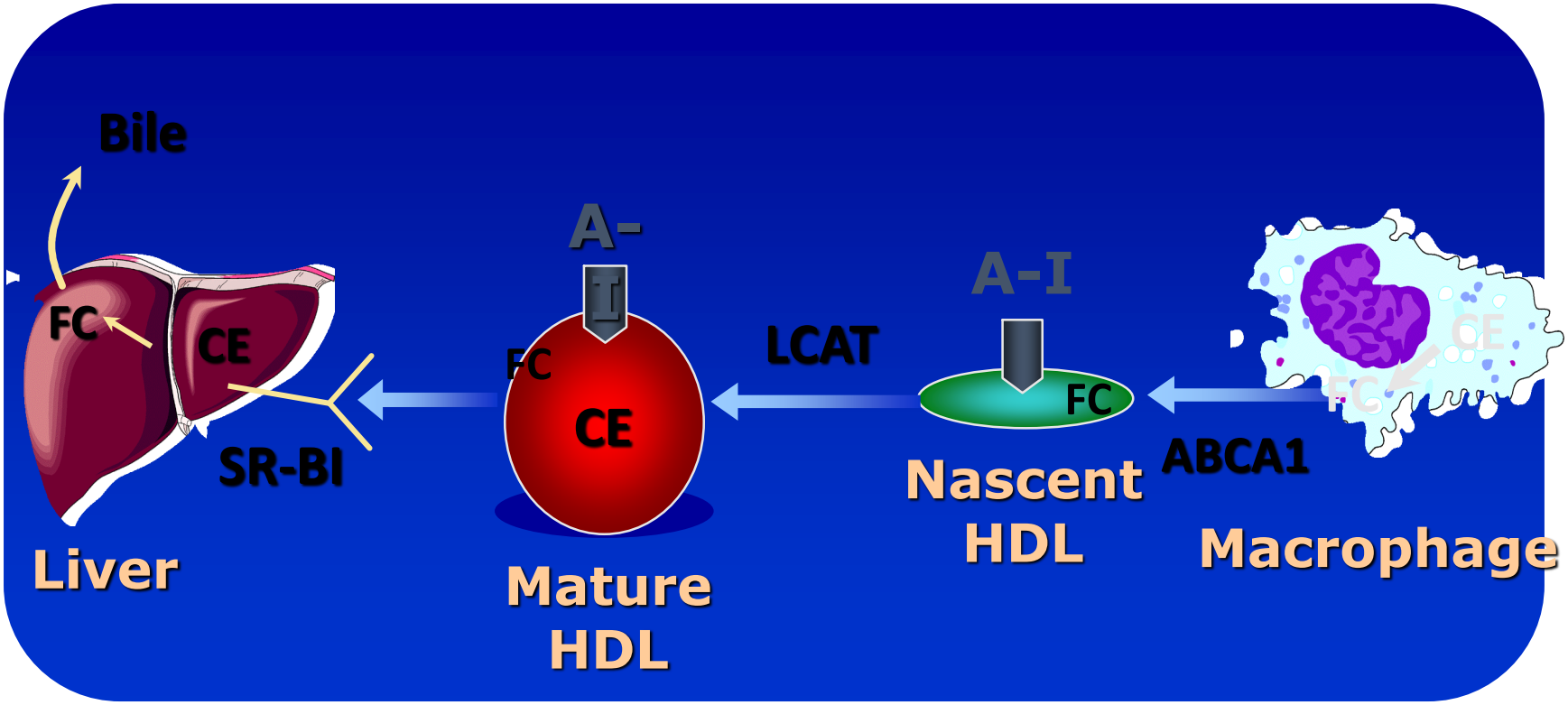
MEASUREMENTS:



Composition of Triglyceride-Rich Lipoproteins (% dry mass)



HDL and Reverse Cholesterol Transport



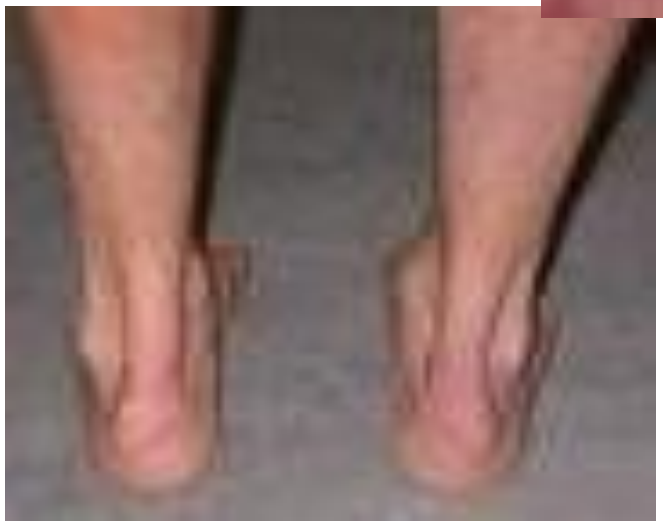
Plasma lipoproteins

Type	Source	Major lipid	Apoproteins	ELFO	Athero-genicity
Chylomicrons	Gut	Dietary TGs	A-I, B-48, C-I, C-III, E	no mobility	– (pancreatitis)
VLDL	Liver	Endogenous TGs	B-100, E, C-II, C-III,	Pre-β	+
IDL	VLDL remnant	Ch esters, TGs	B-100, C-III, E	Slow pre- β	+
LDL	VLDL, IDL	Ch esters	B-100	β	+++
HDL	Gut, liver	Ch esters, PLs	A-I, A-II, C-II, C-III, D, E	α	anti-atherogenic

Hereditary Causes of Hyperlipidemia

- Familial Hypercholesterolemia
  - Codominant genetic disorder, coccurs in heterozygous form
  - Occurs in 1 in 500 individuals
  - Mutation in LDL receptor, resulting in elevated levels of LDL at birth and throughout life
  - High risk for atherosclerosis, tendon xanthomas (75% of patients), tuberous xanthomas and xanthelasmas of eyes.
- Familial Combined Hyperlipidemia
  - Autosomal dominant
  - Increased secretions of VLDLs
- Dysbetalipoproteinemia
  - Affects 1 in 10,000
  - Results in apo E2, a binding-defective form of apoE (which usually plays important role in catabolism of chylomicron and VLDL)
  - Increased risk for atherosclerosis, peripheral vascular disease
  - Tuberous xanthomas, striae palmaris

Physical findings



Fredrickson classification of hyperlipidemias

Phenotype	Lipoprotein(s) elevated	Plasma cholesterol	Plasma TGs	Athero-genicity	Rel. freq.	Treatment
I	Chylomicrons	Norm. to ↑	↑↑↑↑	– pancreatitis	<1%	Diet control
IIa	LDL	↑↑	Norm.	+++	10%	Bile acid sequestrants, statins, niacin
IIb	LDL and VLDL	↑↑	↑↑	+++	40%	Statins, niacin, fibrates
III	IDL	↑↑	↑↑↑	+++	<1%	Fibrates
IV	VLDL	Norm. to ↑	↑↑	+	45%	Niacin, fibrates
V	VLDL and chylomicrons	↑ to ↑↑	↑↑↑↑	+ pancreatitis	5%	Niacin, fibrates

Primary hypercholesterolemias

Disorder	Genetic defect	Inheritance	Prevalence	Clinical features
Familial hyper-cholesterolemia	LDL receptor	dominant	heteroz.:1/500 5% of MIs <60 yr homoz.: 1/1 million	premature CAD (ages 30–50) TC: 7-13 mM CAD before age 18 TC > 13 mM
Familial defective apo B-100	apo B-100	dominant	1/700	premature CAD TC: 7-13 mM
Polygenic hypercholestero lemia	multiple defects and mechanisms	variable	common 10% of MIs <60 yr	premature CAD TC: 6.5-9 mM
Familial hyper-alphalipoprotein emia	unknown	variable	rare	less CHD, longer life elevated HDL

Primary hypertriglyceridemias

Disorder	Genetic defect	Inheritance	Prevalence	Clinical features
LPL deficiency	endothelial LPL	recessive	rare 1/1 million	hepatosplenomegaly abd. cramps, pancreatitis TG: > 8.5 mM
Apo C-II deficiency	Apo C-II	recessive	rare 1/1 million	abd. cramps, pancreatitis TG: > 8.5 mM
Familial hyper-triglyceridemia	unknown enhanced hepatic TG-production	dominant	1/100	abd. cramps, pancreatitis TG: 2.3-6 mM

Primary mixed hyperlipidemias

Disorder	Genetic defect	Inheritance	Prevalence	Clinical features
Familial dysbeta-lipoproteinemia	Apo E high VLDL, chylo.	recessive rarely dominant	1/5000	premature CAD TC: 6.5 -13 mM TG: 2.8 – 5.6 mM
Familial combined	unknown high Apo B-100	dominant	1/50 – 1/100 15% of MIs <60 yr	premature CAD TC: 6.5 -13 mM TG: 2.8 – 8.5 mM

Dietary sources of Cholesterol

Type of Fat	Main Source	Effect on Cholesterol levels
Monounsaturated	Olives, olive oil, canola oil, peanut oil, cashews, almonds, peanuts and most other nuts; avocados	Lowers LDL, Raises HDL
Polyunsaturated	Corn, soybean, safflower and cottonseed oil; fish	Lowers LDL, Raises HDL
Saturated	Whole milk, butter, cheese, and ice cream; red meat; chocolate; coconuts, coconut milk, coconut oil , egg yolks, chicken skin	Raises both LDL and HDL
Trans	Most margarines; vegetable shortening; partially hydrogenated vegetable oil; deep-fried chips; many fast foods; most commercial baked goods	Raises LDL

Causes of Hyperlipidemia

- Diet
- Hypothyroidism
- Nephrotic syndrome
- Anorexia nervosa
- Obstructive liver disease
- Obesity
- Diabetes mellitus
- Pregnancy
- Obstructive liver disease
- Acute heaptitis
- Systemic lupus erythematousus
- AIDS (protease inhibitors)

Secondary hyperlipidemias

Disorder	VLDL	LDL	HDL	Mechanism
Diabetes mellitus	↑ ↑ ↑	↑	↓	**VLDL production ↑, LPL ↓, altered LDL**
Hypothyroidism	↑	↑ ↑ ↑	↓	**LDL-rec.↓, LPL ↓**
Obesity	↑ ↑	↑	↓	**VLDL production ↑**
Anorexia	-	↑ ↑	-	**bile secretion ↓, LDL catab. ↓**
Nephrotic sy	↑ ↑	↑ ↑ ↑	↓	**Apo B-100 ↑ LPL ↓ LDL-rec. ↓**
Uremia, dialysis	↑ ↑ ↑	-	↓	**LPL ↓, HTGL ↓ (inhibitors ↑)**
Pregnancy	↑ ↑	↑ ↑	↑	**oestrogen ↑ VLDL production ↑, LPL ↓**
Biliary obstruction PBC	-	-	↓	**Lp-X ↑ ↑ no CAD; xanthomas**
Alcohol	↑ ↑ **chylomicr. ↑**	-	↑	**dep. on dose, diet, genetics**

When to check lipid panel

- Different Recommendations
  - Adult Treatment Panel (ATP III) of the National Cholesterol Education Program (NCEP)
    - Beginning at age 20: obtain a fasting (9 to 12 hour) serum lipid profile consisting of total cholesterol, LDL, HDL and triglycerides
    - Repeat testing every 5 years for acceptable values

United States Preventative Services Task Force

- Women aged 45 years and older, and men ages 35 years and older undergo screening with a total and HDL cholesterol every 5 years.
- If total cholesterol > 200 or HDL <40, then a fasting panel should be obtained
- Cholesterol screening should begin at 20 years in patients with a history of multiple cardiovascular risk factors, diabetes, or family history of either elevated cholesteral levels or premature cardiovascular disease.

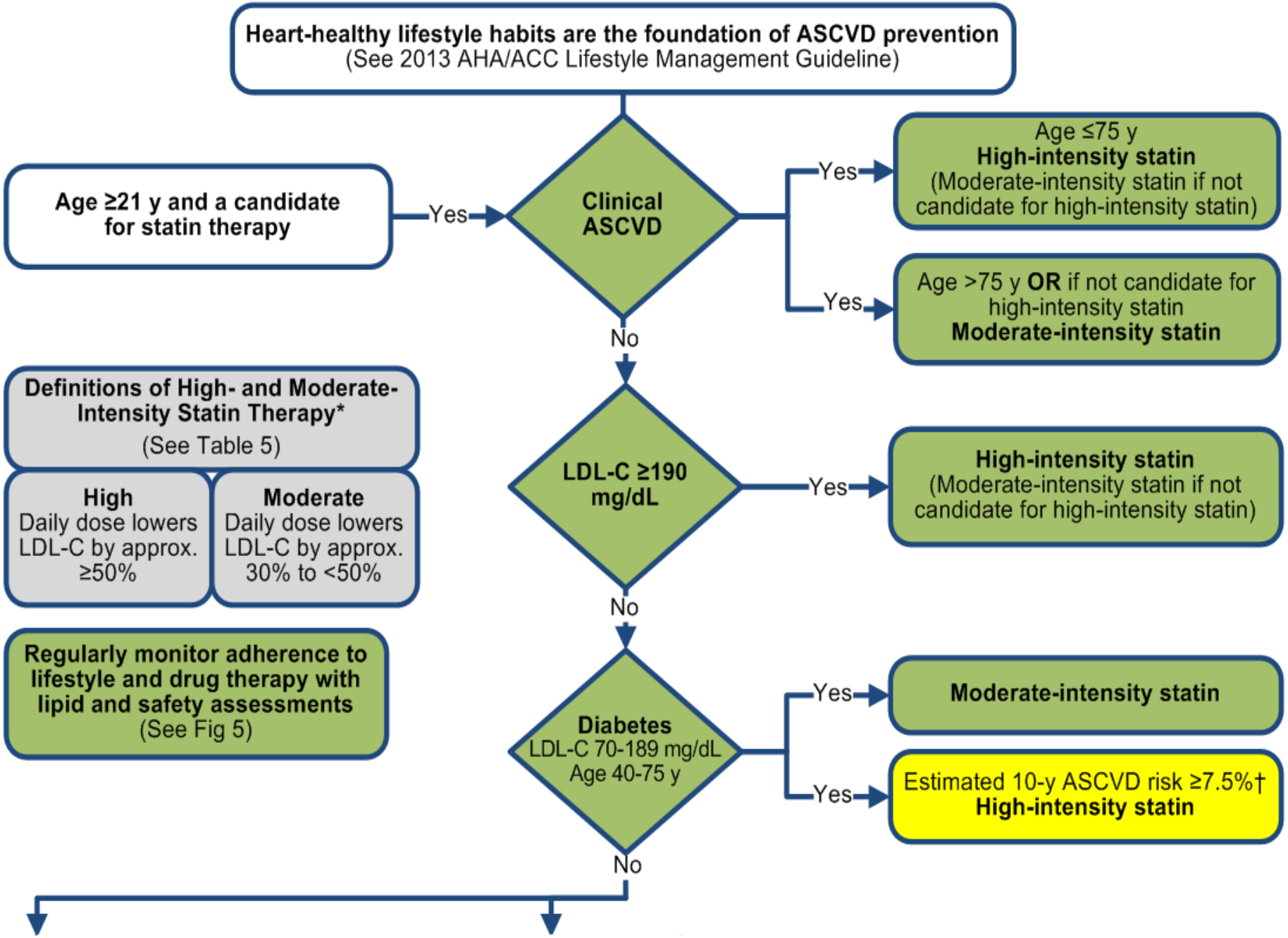
Treatment

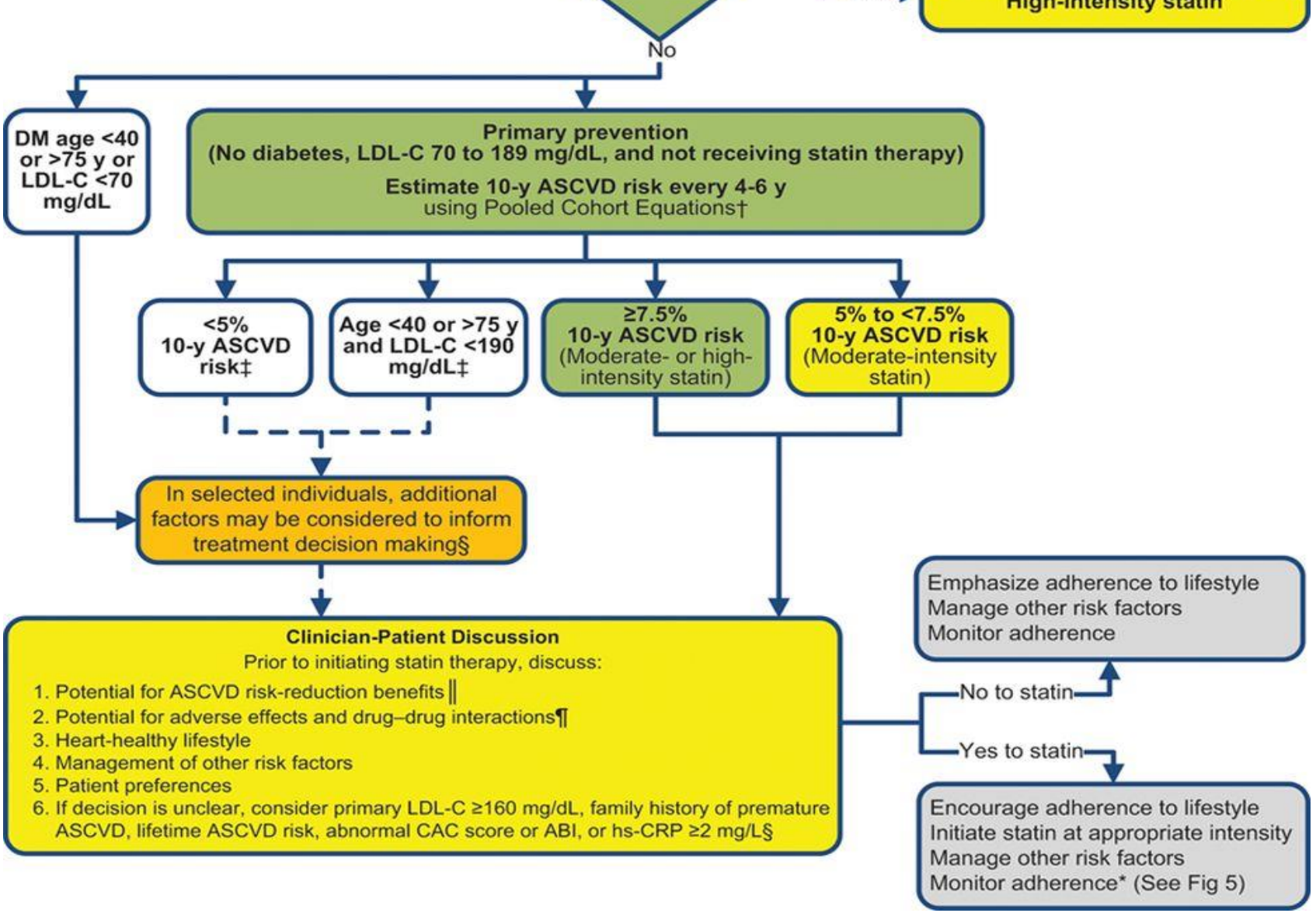
Targets

- LDL: To prevent coronary heart disease outcomes (myocardial infarction and coronary death)

- Non LDL(TC/HDL): To prevent coronary heart disease outcomes (myocardial infarction and coronary death)

- Triglyceride: To prevent **pancreatitis** and may be coronary heart disease outcomes (myocardial infarction and coronary death)


Heart-healthy lifestyle habits are the foundation of ASCVD prevention
(See 2013 AHA/ACC Lifestyle Management Guideline)
Age ≥21 y and a candidate for statin therapy
Yes
Clinical ASCVD
Yes
Age ≤75 y
High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)
Yes
Age >75 y OR if not candidate for high-intensity statin
Moderate-intensity statin
No
Definitions of High- and Moderate-Intensity Statin Therapy*
(See Table 5)
High
Daily dose lowers LDL-C by approx. ≥50%
Moderate
Daily dose lowers LDL-C by approx. 30% to <50%
LDL-C ≥190 mg/dL
Yes
High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)
No
Regularly monitor adherence to lifestyle and drug therapy with lipid and safety assessments
(See Fig 5)
Diabetes
LDL-C 70-189 mg/dL
Age 40-75 y
Yes
Moderate-intensity statin
Yes
Estimated 10-y ASCVD risk ≥7.5%†
High-intensity statin
No



Stone N J et al. Circulation. 2014;129:S1-S45

American Heart Association.

Guideline of therapy

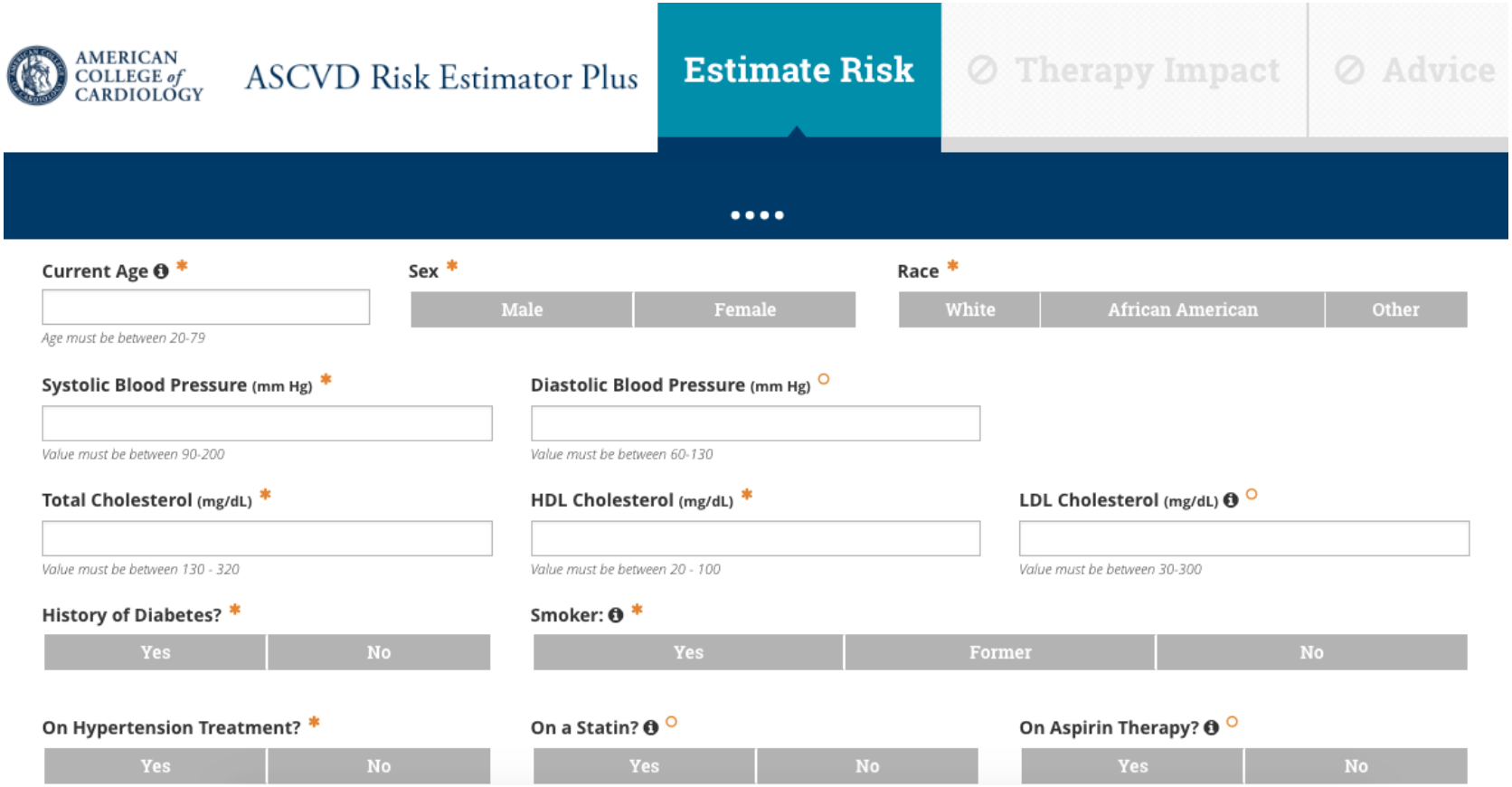
Age	Risk Factors	Statin Intensity*
>29 Age	ASCVD	High
>29 years	LDL >190 mg/dl (4.9 mmol/l)	High
NO DM LDL <190	estimate 10-year risk for ASCVD <5%	No
	estimate 10-year risk for ASCVD 5-7.5%	Moderate
	estimate 10-year risk for ASCVD >7.5%	High

Estimate 10-year risk for ASCVD

http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/

AGE
SBP/DBP
T cholesterol
HDL
LDL
DM
Smoking
On Anti HTN
On statin
On asprin

Estimate 10-year risk for ASCVD



Recommendations in DM

Age	Risk Factors	Statin Intensity*
<40 years	None	None
	ASCVD risk factor(s)	Moderate or high
	ASCVD	High
40–75 years	None	Moderate
	ASCVD risk factors	High
	ACS & LDL ≥50 or in patients with history of ASCVD who can't tolerate high dose statin	Moderate + ezetimibe
>75 years	None	Moderate
	ASCVD risk factors	Moderate or high
	ASCVD	High
	ACS & LDL ≥50 or in patients with history of ASCVD who can't tolerate high dose statin	Moderate + ezetimibe

Statin Treatment

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL-C, on average, by approximately ≥50% Atorvastatin (40†)-80 mg Rosuvastatin 20 (40) mg	Daily dose lowers LDL-C, on average, by approximately 30% to <50% Atorvastatin 10 (20) mg Rosuvastatin (5) 10 mg Simvastatin 20-40 mg‡ Pravastatin 40 (80) mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 2-4 mg	Daily dose lowers LDL-C, on average, by <30% Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg

Jammah

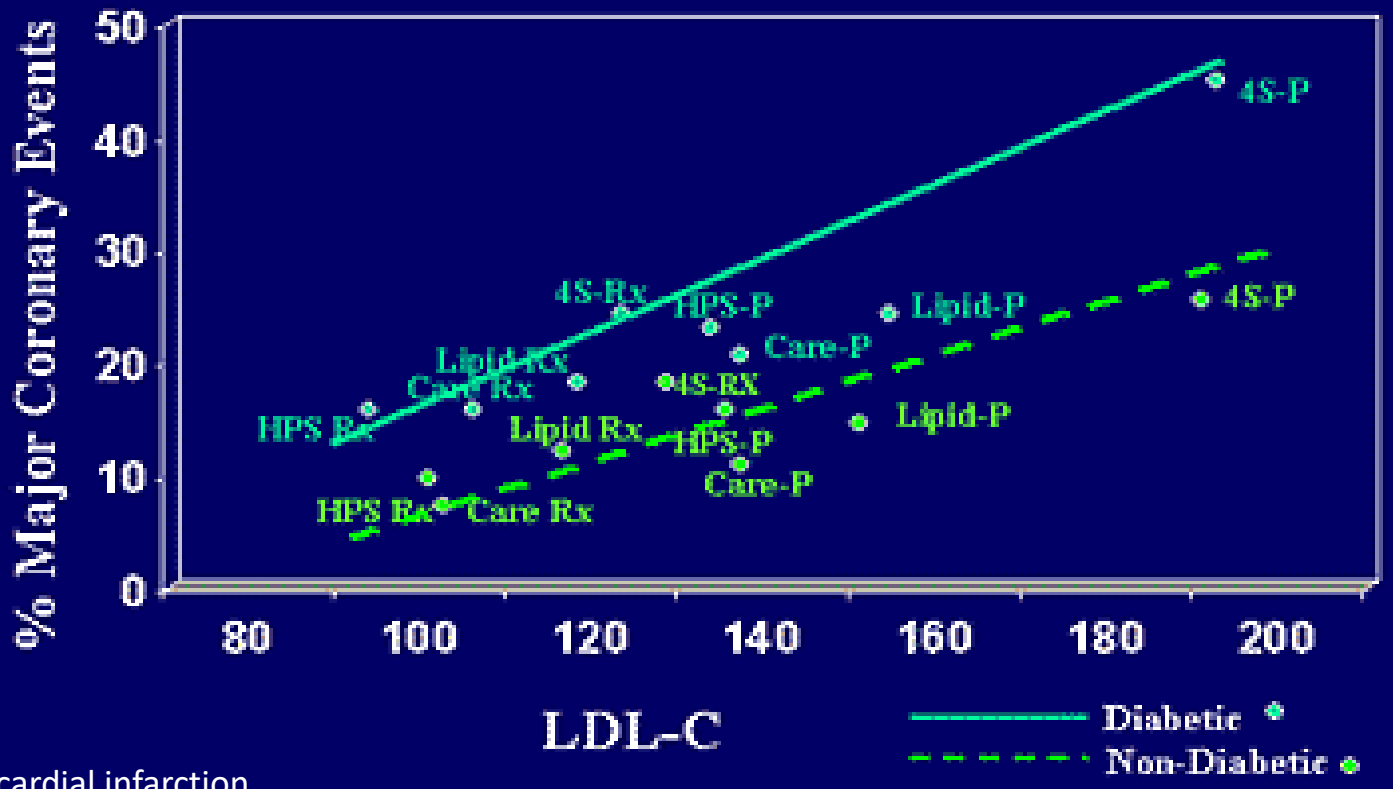
Treatment of Hyperlipidemia

- Lifestyle modification
  - Low-cholesterol diet
  - Exercise
  - Smoking
  - Alcohol

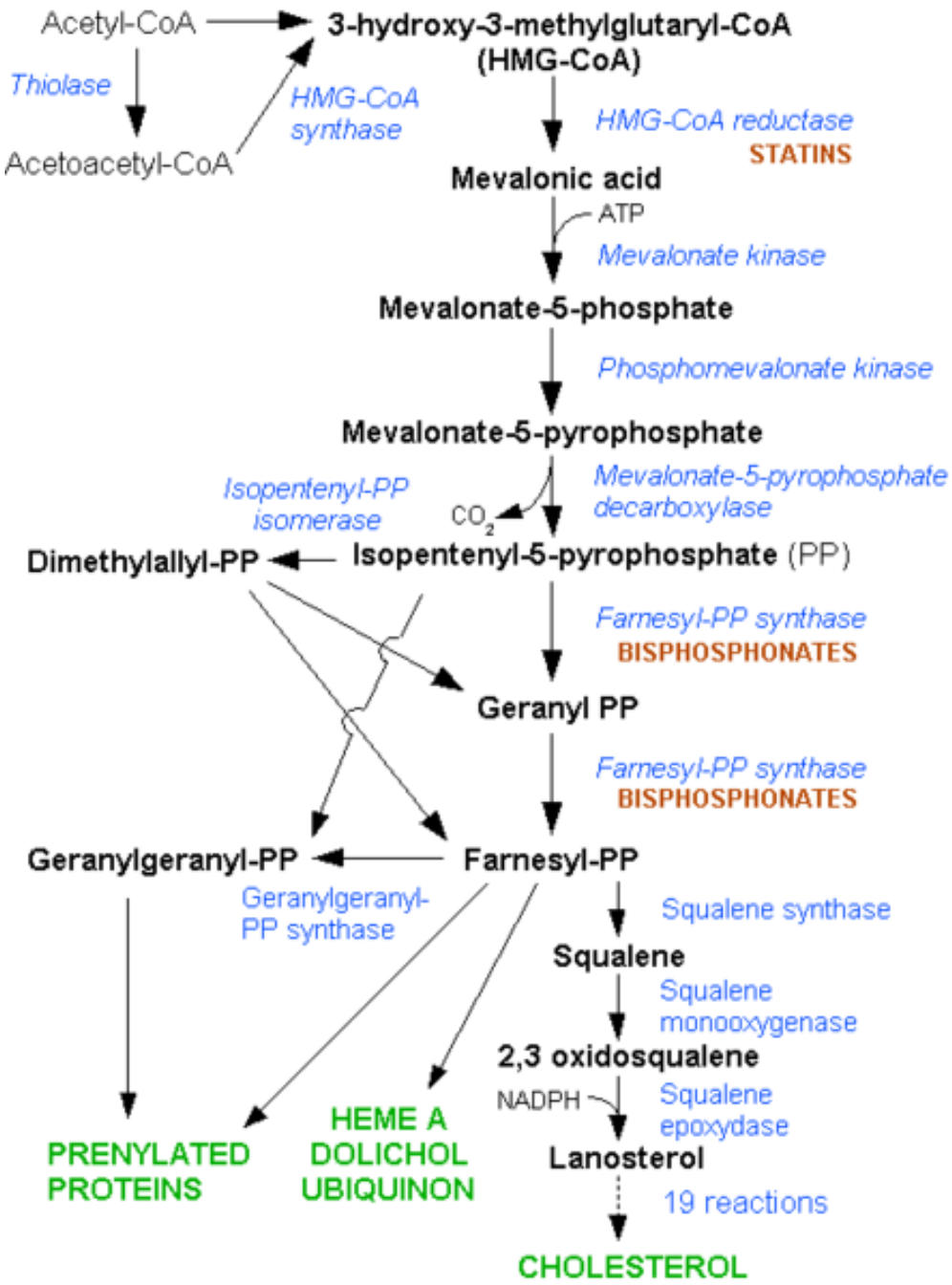
Medications for Hyperlipidemia

Drug Class	***Agents***	***Effects (% change)***	***Side Effects***
HMG CoA reductase inhibitors	**Statins**	**↓LDL (18-55),↑ HDL (5-15) ↓ Triglycerides (7-30)**	**Myopathy, increased liver enzymes**
Cholesterol absorption inhibitor	**Ezetimibe**	**↓ LDL(14-18), ↑ HDL (1-3) ↓Triglyceride (2)**	**Headache, GI distress**
Nicotinic Acid		**↓LDL (15-30), ↑ HDL (15-35) ↓ Triglyceride (20-50)**	**Flushing, Hyperglycemia, Hyperuricemia, GI distress, hepatotoxicity**
Fibric Acids	**Gemfibrozil Fenofibrate**	**↓LDL (5-20), ↑HDL (10-20) ↓Triglyceride (20-50)**	**Dyspepsia, gallstones, myopathy**
Bile Acid sequestrants	**Cholestyramine**	**↓ LDL↑ HDL No change in triglycerides**	**GI distress, constipation, decreased absorption of other drugs**
PCSK9	**Evolocumab Alirocumab**	**↓ LDL (50-60%)**	**injection-site reactions, muscle pain, neurocognitive adverse events. These included memory impairment and confusion**

Statin Risk Reduction in Diabetic Patients and Non-Diabetic Patients



MI = myocardial infarction.


Acetyl-CoA
3-hydroxy-3-methylglutaryl-CoA
(HMG-CoA)
Thiolase
HMG-CoA
synthase
Acetoacetyl-CoA
HMG-CoA reductase
STATINS
Mevalonic acid
ATP
Mevalonate kinase
Mevalonate-5-phosphate
Phosphomevalonate kinase
Mevalonate-5-pyrophosphate
Isopentenyl-PP
isomerase
CO2
Mevalonate-5-pyrophosphate
decarboxylase
Dimethylallyl-PP
Isopentenyl-5-pyrophosphate (PP)
Farnesyl-PP synthase
BISPHOSPHONATES
Geranyl PP
Farnesyl-PP synthase
BISPHOSPHONATES
Geranylgeranyl-PP
Farnesyl-PP
Geranylgeranyl-
PP synthase
Squalene synthase
Squalene
Squalene
monooxygenase
2,3 oxidosqualene
NADPH
Squalene
epoxydase
Lanosterol
19 reactions
PRENYLATED
PROTEINS
HEME A
DOLICHOL
UBIQUINON
CHOLESTEROL

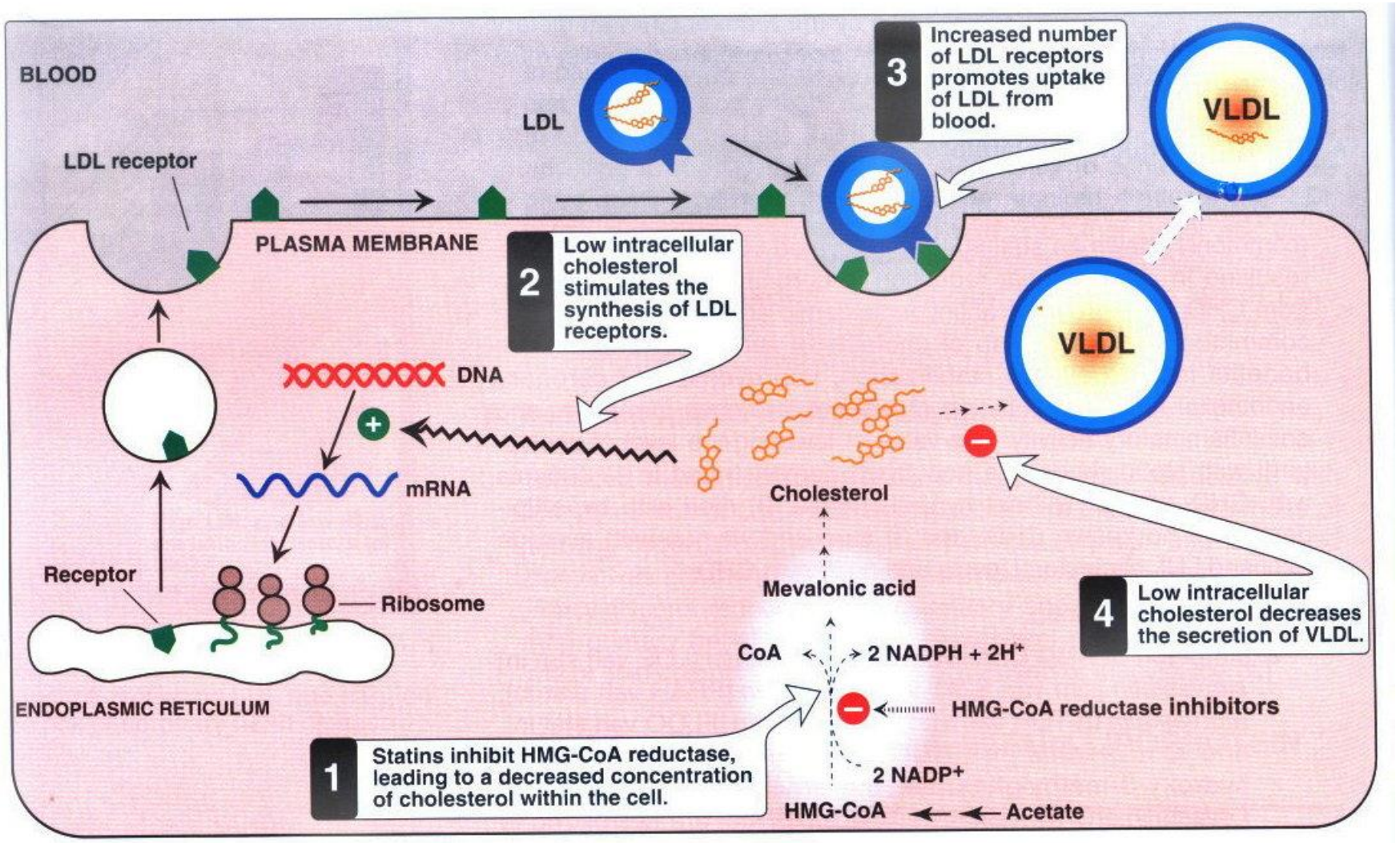


Figure 21.5
Inhibition of HMG-CoA reductase by the statin drugs.

Table 1: Assessment and action strategies for elevated plasma triglyceride concentrations [TG]

[TG], mmol/L	Step	Action and comments	Retest interval, mo*
< 2		Continue current management • Reassess lipid profile regularly, to ensure that [LDL-C] is at target	6-12
≥ 2, < 5	1.	Therapeutic lifestyle measures • Weight control • Reduce dietary fat, simple sugars • Reduce alcohol intake • Increase physical activity Reassess lipid profile regularly, to ensure that [LDL-C] is at target	3-6
	2.	Manage other secondary factors • Control glycemia, if diabetic • Reassess medications; consider lipid-neutral alternatives	
	3.	Consider pharmacologic treatment • Intensify LDL-lowering (e.g., statin therapy) • Fish oil (omega-3 fatty acid) • Niacin (e.g., extended release)	

Table 1: Assessment and action strategies for elevated plasma triglyceride concentrations [TG]

≥ 5, < 10	4. Intensify steps 1-3, above • [LDL-C] cannot be estimated when [triglycerides] > 5 mmol/L • Apolipoprotein B determination might be helpful	2-3
	5. Consider fibrate therapy, e.g., • Bezafibrate (Bezalip) 400 mg/d • Fenofibrate — Lipidil micro 200 mg/d — Lipidil supra 160 mg/d — Lipidil EZ 145 mg/d • Gemfibrozil (Lopid) 600-1200 mg/d	
≥ 10	6. Further intensify steps 1-3 With acute pancreatitis: • Very-low-fat diet (10%-15% of energy intake) • Cessation of alcohol • Insulin, if indicated for glycemic control • Admit patient to hospital — Nothing by mouth: IV fluid replacement — Plasma exchange is unhelpful	1-2
	7. Initiate fibrate therapy • Monitor serum [creatinine]	
	8. Consider specialist referral	

George Yuan, Khalid Z. Al-Shali, Robert A. Hegele
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THANK YOU

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See you in 5th year MED-441 Course